REMARKS

Amendments

The claim numbers are amended to correct an error in the original numbering of the claims. Specifically, no claim 12 was originally presented. See also the Examiner's comment at the top of page 2 of the Office Action of May 23, 2003.

In addition, to facilitate prosecution, Applicants have cancelled claims which specify that the additional chemotherapeutic agent is other than doxorubicin. New claims 63-71 are directed to further aspects of Applicants' claimed invention. See, for example, the original claims; page 7, lines 15-25; page 9, lines -8 and 24-26; page 10, line 1; and page 22.

Election

Firstly, Applicants wish to point out a typographical error in the Election filed April 17, 2003. At page 4 of that paper, the last sentence in the first paragraph under the heading "Election" should read: Applicants understand that examination will **now** continue pursuant to MPEP § 809.02(c).

On the top of page 2 of the Office Action of May 23, 2003, it is stated that claims 14-18, 22-24, 27-31, 38-45, 47-49 and 57 are withdrawn from consideration as being drawn to a non-elected invention. Applicants disagree that all of these claims are properly withdrawn from consideration.

Claims 14-18 depend from claim 11. Each of claims 14-18 encompass the elected embodiment of β-L-OddC and doxorubicin. Similarly, claims 27-31 also encompass the elected embodiment (although it is noted that these claims have now been cancelled). Claims 41-45 also read on the elected embodiment, as does claim 57. No rationale is presented in the Office Action as to why these claims are not grouped with the non-elected claims. It is respectfully requested that claims 14-18, 41-45 and 57 be examined together with the other elected claims.

Rejection Under 35 USC § 103 in view of Chu et al. (WO 96/07413)

All the claims designated as elected have been rejected as allegedly being obvious under 35 U.S.C. § 103 in view of Chu et al. (WO 96/07413). This rejection is respectfully traversed.

At page 6, lines 18-28, Chu et al. discloses that (-)-(2S, 4S)-1-(2-hydroxymethyl-1,3-dioxolan-4-yl) cytosine, also known as (-) OddC, has activity against cancer cells. Thereafter,

Chu et al. lists general examples of such cancers including lung, breast, bladder, pancreas, lymphoma and leukemia.

At page 7, line 30- page 8, line 11, Chu et al. disclose that the compounds described therein can be administered in combination or alternation with other anti-tumor agents. Chu et al. provides a long list of specific agents including nitrogen mustards, ethyleneimine compounds, alkyl sulfates, growth factors, and alpha, beta, and gamma interferons, as well as "doxirubicin." As a specific combination, Chu et al. describe the combination of (-)-OddC and THU, i.e., tetrahydrouridine, a cytidine deaminase inhibitor. See page 8, lines 22-29.

In light of this disclosure in Chu et al., it is asserted that it would be obvious to combine β-L-OddC with doxorubicin to treat leukemia. However, it is respectfully submitted that the rejection fails to establish sufficient motivation that would lead one of ordinary skill in the art, in light of the disclosure of Chu et al., to an embodiment in accordance with Applicants' claimed invention.

For example, the rejection fails to set forth the motivation that would lead one of ordinary skill in the art to first select leukemia from the long list of possible tumors of possible cancers presented at page 6 of the Chu et al. disclosure and then further select doxorubicin to be used in combination with β-L-OddC, in light of the long list of anti-tumor agents presented in the paragraph bridging pages 7 and 8.

The mere ability to modify the disclosure of a reference does not, in and of itself, establish obviousness. Instead, the rejection must set forth a sufficient motivation that would lead one of ordinary skill in the art to make such a modification so as to arrive in an embodiment of a claimed invention. Here, no motivation is presented. The rejection merely alleges that it would be obvious to use two cancer treatment agents together. But, there is no motivation presented as to why one would select leukemia, as the cancer to be treated, and then further select doxorubicin as the anti-tumor agent to be used in combination based on a long list of specific anti-tumor agents encompassing a large number of diverse compounds. The case cited by the Examiner, *In re Sussman*, 58 USPQ 262 (CCPA 1943), dealt with a shaving preparation and a combination of components known for use in skin applications. The case did not deal with combinations of agents administered internally, let alone combing agents for the treatment of a disease, let alone combing agents for the treatment of cancer.

Moreover, contrary to the assertion in the rejection, the data presented in Table 1 on page 22 of the specification, does represent an unexpected result. The cells of Group 2 were treated with β-L-OddC at a dose of 1 mg/kg, which resulted in a 55% augmentation of

survival time. The cells of Group 3 were treated with doxorubicin at a dose of 0.2 mg/kg, resulting in only a 25% augmentation of survival time. Yet, when these two agents were combined at these same dosages in the cells of Group 4, i.e., β-L-OddC at 1 mg/kg and doxorubicin at 0.2 mg/kg, the augmentation of survival time was the same as experienced by the cells treated with β-L-OddC alone, i.e., a 55% augmentation in survival time. The combination of doxorubicin with β-L-OddC had no additive affect for the cells of Group 4.

However, when doxorubicin was combined at a higher dosage with β-L-OddC, the result was an augmentation in survival time that was greater than either β-L-OddC or doxorubicin administered alone at the same dosages. Compare the augmentation survival times for cell Groups 2, 5 and 6. Such results are clearly in no way suggested by the disclosure of Chu et al.

In Example 11, Chu et al. asserts that (-)-OddC was evaluated in NCI's cancer screening program. As shown in Table 2 at page 35, the leukemia cell lines are identified as CCRF-CEM, RL-60(TB), K-562, BSOL T-4, RPMI-2.26, and SR. Applicants' have attempted to find out the identities of the cell lines, some of which are apparently incorrectly named by Chu et al. CCRF-CEM is an acute lymphoblastic cell line. It is believed that RL-60(TB) was intended to be HL-60, which is an acute promyelocytic leukemia cell line. K-562 is a chronic myelogenous leukemia (CML) cell line. It is believed that BSOLT-4 was intended to be MOLT-4, an acute lymphoblastic leukemia cell line. RPMI-2.26 is assumed to be a reference to RPMI-82.26, a human hematopoietic cell line obtained from a patient with multiple myeloma. Finally, SR is a B-lymphoblastoid cell line. Thus, none of these cell lines appear to be an acute myelogenous leukemia cell line. Compare claim 13.

Moreover, there is clearly no suggestion from Chu et al. that the (-) OddC, alone or in combination with doxorubicin, can be used for treating leukemias which have been found to be resistant or refractory to ara-C, also known as cytarabine, (1-ß-D-arabinofuranosyl-cytosine), which like (-)OddC is a cytosine nucleoside. Thus, there is no motivation or suggestion to use the combination (-) OddC and doxorubicin in treating a patient which has been previously treated with ara-C. Compare applicants' claim 64. Similarly, there is no suggestion by Chu et al. to use (-)OddC, alone or in combination with doxorubicin, to treat a patient suffering from a leukemia which is non-responsive to treatment with other chemotherapeutic agents. Compare applicants' claim 65. These claims describe the treatment of patient classes which are in no manner suggested by the disclosure of Chu et al. Similarly, these claims describe treatments of leukemias that are not suggested by Chu et al.

In view of the above remarks, it is respectfully submitted that Chu et al. fails to establish sufficient motivation which would lead one of ordinary skill in the art to modify the disclosure of Chu et al. in such a manner as to arrive at an embodiment in accordance with Applicants' claimed invention. Withdrawal of the rejection under 35 U.S.C. § 103 is respectfully requested.

Favorable consideration of the instant application is respectfully requested.

Respectfully submitted,

Brion P. Heaney (Reg. No. 32,542)
Attorney for Applicants
MILLEN, WHITE, ZELANO & BRANIGAN, P. C.
2200 Clarendon Boulevard, Suite 1400
Arlington, Virginia 22201
(703) 812-5308
Internet address: heaney@mwzb.com

Filed: October 23, 2003